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Antibiotic Prophylaxis for Pit Viper Envenomation: Prospective, Controlled Trial

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Abstract. The efficacy of prophylactic antibiotics for preventing infectious complications at the site of pit viper envenomation has not been well studied. We undertook a prospective, controlled trial of antibiotic treatment versus no antibiotic treatment among 114 victims of crotalid envenomation in Ecuador's Amazon rain forest. A group of 59 patients received intravenous gentamicin and chloramphenicol, and 55 patients did not. All other aspects of care were identical. There were no statistically significant differences between antibiotic-treated and untreated patients with regard to demographics, delay in treatment, clinical and laboratory evidence of severity of envenomation, or use of antivenin. Nine abscesses occurred, six in the antibiotic-treated group and three in the untreated group. The results of this study did not show any statistically significant differences in outcome in terms of the number of abscesses that occurred between antibiotic-treated and untreated patients. Based on this lack of differences, routine use of prophylactic antibiotics for prevention of infectious complications of crotalid envenomation cannot be recommended.

Bacterial infection at the site of envenomation is a major cause of morbidity with pit viper bites. These severe infections occur most commonly on bitten extremities of young, otherwise healthy individuals. The resultant functional impairment and loss of productivity is substantial. Currently, there is no treatment modality that has been demonstrated to prevent the occurrence of bacterial infection at the site of pit viper envenomation.

Most cases of snake envenomation in the Western Hemisphere are due to bites of snakes of the family Viperidae, subfamily Crotalidae, also known as pit vipers. Crotalidae is represented in the United States by the genera *Crotalus* (rattlesnakes), *Agkistrodan* (moccasins), and *Sistrurus* (massasaugas and pygmy rattlers). In Ecuador, Crotalidae is represented by the genera *Bothrups* and *Lachesis* [1].

Crotalid venom is a complex mixture of enzymatic and nonenzymatic peptides designed to digest the tissue of injected prey. When humans are bitten, this digestive process results in red blood cell extravasation, hypoxia, and necrosis at the site of envenomation, producing an ideal environment for bacterial proliferation. At the time of envenomation a potent inoculum of aerobic and anaerobic bacteria is introduced by the snake's fangs. The combined tissue-destructive effects of venom and synergistic bacterial infection lead to abscess formation, necrotizing myofasciitis, or both at the site of envenomation in 7% to 15% of pit viper bites [2, 3].

Antivenin has been shown to decrease edema but to have no effect on necrosis at the site of the bite [4]. Early débridement and fasciotomy of upper extremity pit viper wounds reduces hand deformities [5], but its effect on abscess formation remains unknown. Prophylactic antibiotics have been advocated by some authors but dismissed by others [6–8]. The continuing controversy regarding the role of prophylactic antibiotics in the treatment of pit viper envenomation is the result of a lack of data with regard to the efficacy of their use.

The current study is a prospective, controlled trial to determine whether use of prophylactic antibiotics can decrease the incidence of infectious complications at the site of pit viper envenomation. Epidemiologic features of snakebite in the population of eastern Ecuador's tropical rain forest have been previously reported [9], as has the bacteriology and antibiotic sensitivities of snakebite abscess in this group of patients [10].

Hospital Vozandes Oriente (HVO) is a primary care and referral hospital serving the population of Ecuador's Amazon rain forest. Crotalid envenomation is a major health problem in this region. One of the indigenous groups represented in this study has previously been documented as having the highest incidence and mortality from snakebite reported anywhere in the world [11].

Methods

All patients arriving at HVO between October 1, 1990 and June 30, 1993 with a history of snakebite who demonstrated clinical or laboratory evidence of envenomation were included in the study. Clinical evidence consisted of physical findings indicative of local effects of envenomation, such as fang marks, edema, or ecchymoses or systemic effects (i.e., bleeding). Exclusion criteria were an interval between the time of envenomation and arrival at HVO of more than 72 hours (4 patients) and death within 72 hours of the bite (2 patients). A total of 114 patients were thus selected for study. Of the 114 study patients, 59 were randomly assigned to receive antibiotics (group I), and the remaining 55 patients did not (group II). No placebo was given.

Antibiotic administration was begun in the emergency room

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Table 1. Demographics.

Characteristic	Group I	Group II
Gender		
Male	34	29
Female	25	26
Age		
Median age (years)	18	23
Range (years)	3–62	4–84
Ethnic group		
Indigenous	50	44
Nonindigenous	9	11

and continued for 24 hours. The antibiotic regimen consisted of gentamicin 1 mg/kg IV for adults and 2 mg/kg IV for children every 8 hours and chloramphenicol 12 mg/kg IV every 6 hours. All other aspects of care were identical between the two groups.

All patients received tetanus prophylaxis in the form of tetanus toxoid or human tetanus immunoglobulin depending on their prior immunization status. All patients were admitted for observation, intravenous hydration, and elevation of the bitten part. Administration of antivenin was determined by the attending physician in accordance with clinical severity of envenomation and subject to limited availability of antivenin.

Urgent operation for decompression of compartment syndrome was performed based on clinical criteria. Clinical evidence of abscess or necrotizing fasciitis was determined by the lone general surgeon at HVO. All patients thought to manifest signs and symptoms of infectious complications at the site of envenomation underwent operative débridement.

Aerobic cultures were obtained from all surgical wounds. The capability to perform anaerobic cultures was not available.

Statistical analysis of the data consisted of descriptive parametric statistics to establish similarity between the study and control groups, chi-square analysis to detect differences between the groups, and Student's *t*-test to compare means. Significance testing was established at the $p = 0.05$ level for one-tailed tests. Power analysis of the key variables was performed with the finding of 61% experimental power and a probability of a type II error of 39%.

Results

Herpetology

Of the 114 study patients, 43 were able to positively identify the offending snake. All 43 identified snakes were of the genus *Bothrups*.

Demographics

There were 63 males and 51 females in the study group. Eighty-two percent of patients were members of one of the three culturally and linguistically distinct indigenous groups in the region. The remaining 18% were of mixed Spanish and indigenous heritage. Ages ranged from 3 to 84 years (median 22 years). Comparison of antibiotic-treated (group I) and untreated (group II) patients showed no significant differences in demographic features (Table 1).

Table 2. Bacteriology.

Bacterium	Group I	Group II
Escherichia coli	3	
Klebsiella	1	1
Enterobacter		1
Proteus		1
Staphylococcus aureus	3	1

Delay in Treatment

Fifty-three patients (47%) arrived for treatment within 6 hours of the time of the bite, and 87% of all patients arrived within 24 hours after the bite. Delays in treatment were related to transportation difficulties. Most of the indigenous patients treated at HVO live in remote areas of the tropical rain forest where vehicular transportation is not available. There was no statistically significant difference between groups I and II with regard to delay of treatment ($T = -0.066$, $df = 109.5$, $p = 0.947$).

Clinical and Laboratory Signs of Envenomation

Edema was present on physical examination in 102 patients, and 77 patients demonstrated clinical evidence of bleeding from a variety of sites as follows: bite site 50, gingiva 38, gastrointestinal tract 22, genitourinary tract 6, and miscellaneous sites 8. A total of 104 patients had prothrombin times measured, and 89 of them were greater than 15 seconds.

Comparisons between groups I and II regarding clinical and laboratory evidence of severity of envenomation show no statistically significant difference between the groups in terms of the presence of edema (chi-square = 0.009, $df = 1$, $p = 0.926$), clinical evidence of bleeding (chi-square = 0.212, $df = 1$, $p = 0.646$), or abnormal prothrombin time (chi-square = 1.948, $df = 1$, $p = 0.163$).

Treatment

Forty-three of the fifty-nine patients (73%) in group I received antivenin (a total of 95 units, mean 2.0 units per patient). Forty-one of the fifty-five patients (75%) in group II received a total of 86 units of antivenin (mean 2.2 units per patient). There was no statistically significant difference between groups in mean number of units of antivenin administered ($T = 0.261$, $df = 64$, $p = 0.795$).

Eleven patients required fasciotomy because of clinical evidence of compartment syndrome. Six of these patients were in group I and five in group II.

Abscess

Nine abscesses with or without necrotizing fasciitis occurred in the study population. One patient was noted at operation to have gas bubbles in the infected tissue. No patients manifested clinical evidence of tetanus.

All abscess patients had bacterial isolates on aerobic cultures. Seven patients had pure isolates, and two patients had mixed isolates. Of the 11 bacterial isolates, there were 7 gram-negative rods and 4 gram-positive cocci (Table 2).

Antibiotic sensitivity studies showed that all gram-negative rods and all gram-positive cocci were sensitive to gentamicin. All gram-negative rods except one were sensitive to chloramphenicol. Gram-positive cocci were not tested for sensitivity to chloramphenicol.

Six of the nine abscesses occurred among the 59 patients of group I (10.2%). Three abscesses occurred among the 55 patients of group II (5.5%). This difference in incidence of infectious complications at the site of envenomation between antibiotic-treated and untreated patients was not statistically significant (Pearson chi-square with Yates correction = 0.343, $df = 1$, $p = 0.558$). Of the antibiotic-treated patients who developed abscesses, four patients received their first dose of antibiotic within 8 hours from the time of the bite and two of these patients within the first 4 hours.

Discussion

The frequent occurrence of infectious complications at the site of pit viper bites is the result of the synergistic effects of envenomation and contamination with tissue-destructive bacteria. Although tissue necrosis without infection ("dry gangrene") does occur, more commonly infection supervenes [9]. That the incidence of infection is not higher may be related to laboratory evidence suggesting that crotalid venom may itself exhibit antibacterial activity [12].

Currently there is no treatment modality that has been proved effective for preventing infectious complications at the site of pit viper envenomation. The efficacy of antivenin in combating the systemic effects of Crotalid venom has been well demonstrated. However, laboratory experiments fail to demonstrate any significant effect of antivenin administration in preventing tissue necrosis and its infectious sequelae at the site of pit viper envenomation [4].

In the only controlled clinical trial of antivenin administration for treatment of pit viper bites in humans, Reid et al. reported that "specific antivenene [*sic*] is very effective in combating systemic poisoning following bites of the pit viper *A. rhodostoma* but does not appear to help local poisoning" [13].

In our study no attempt was made to control antivenin administration as a variable. Use of antivenin depended on physician judgment based on the interval from time of bite until arrival at HVO as well as clinical and laboratory evidence of the severity of the systemic poisoning. Limited availability of antivenin resulted in administration of doses lower than those recommended by product manufacturers. Retrospective review of antivenin administration between the antibiotic-treated and untreated groups in our study demonstrated no statistically significant difference in the mean number of units administered ($T = 0.261$, $df = 64$, $p = 0.795$).

Early surgical débridement has been shown to lower rates of hand deformity at the site of envenomation [5], but it has never been shown to decrease the incidence of infectious complications at the site of the bite. Nearly 90% of victims of pit viper envenomation recover completely without the need for surgical intervention [9]. Currently there are no reliable criteria for predicting which patients will benefit from early surgical intervention.

The efficacy of prophylactic antibiotics in preventing infectious morbidity in cases of pit viper envenomation has not been well studied. The effective use of antimicrobial prophylaxis in decreasing the infectious morbidity of clean and clean-contaminated surgical procedures is well documented. Important principles include administration of adequate doses of appropriate antibiotics during the 2 hours prior to creation of the surgical wound [14, 15]. Initiation of antibiotics prior to bacterial contamination is not practical in traumatic wounds. However, presumptive antibiotic treatment administered as soon as possible after injury has been shown to lower infectious morbidity in cases of abdominal trauma [16]. Aminoglycoside-based combinations have been the "gold standard" against which various broad-spectrum single agents have been compared. Short-course antibiotic prophylaxis (i.e., 12 hours) has been shown to be as efficacious as prolonged coverage [17].

Laboratory investigations demonstrate that the mouth flora of pit vipers reflect the fecal flora of their prey. Aerobic isolates of venom and oral cavities of North American pit vipers reveal a preponderance of enteric and coliform organisms. Histotoxic *Clostridium* has been found to be the most common anaerobic genus isolated [18, 19].

The selection of gentamicin and chloramphenicol for use in the present study was based on these clinical and laboratory findings as well as antibiotic sensitivities among 38 cases of snakebite abscess previously reported from our hospital [10].

Despite the similarity with regard to demographic features, delay of treatment, and clinical and laboratory evidence of the severity of the envenomation between the study and control groups, abscess formation occurred twice as often in antibiotic-treated patients as in those who did not receive antibiotics. This difference was not statistically significant. It is possible that earlier initiation of antibiotics would demonstrate an effect on lowering infectious complications of crotalid envenomation. From a worldwide perspective, our population is representative of groups who are at highest risk of snakebite (i.e., isolated populations in remote, rural locations), and any treatment regimen that is impractical for this group is of limited benefit.

In conclusion, antibiotic administration is not indicated as initial therapy for pit viper envenomation. Use of antibiotics in this setting does not prevent infectious complications of envenomation, is not cost-effective, and may serve only to select out more resistant organisms. Antibiotic administration should be reserved for treatment of established infections. When thus used, antibiotic selection should be based on results of culture and sensitivity studies. Antibiotics may also be indicated perioperatively in patients undergoing early débridement of snake bite wounds.

Résumé

L'efficacité de l'antibioprophylaxie dans la prévention des complications infectieuses du site de morsure de vipères n'est pas bien étudiée. Nous avons entrepris une étude prospective contrôlée comparant l'antibioprophylaxie et l'absence d'antibioprophylaxie chez 114 victimes de morsure de crotales dans la Forêt tropicale amazonienne, en Equateur. Cinquante neuf patients ont reçu de la gentamycine et du chloramphénicol, alors que 55 patients n'ont pas eu d'antibioprophylaxie. Tous les autres aspects des soins étaient similaires. Il n'a pas été trouvé de différence en ce qui concerne les caractéristiques des patients, le délai de la mise en route du traitement, les signes cliniques ou paracliniques de sévérité, d'envenimation ou l'utilisation de sérum antivénin. On a observé neuf cas d'abcès, six dans le groupe traité, trois dans le groupe non traité. Les résultats de cette étude n'ont pas objectivé de différence statistiquement significative entre les patients traités et les patients non traités par l'antibiothérapie prophylactique L'utilisation de l'antibioprophylaxie pour prévenir des complications infectieuses après morsures de serpents venimeux n'est pas préconisée de façon systématique.

Resumen

La eficacia de los antibióticos profilácticos en la prevención de complicaciones sépticas en la mordedura de serpientes venenosas no ha sido bien estudiada. Hemos realizado un estudio prospectivo y controlado sobre el tratamiento versus no tratamiento con antibióticos en 114 víctimas de mordedura por crotalídeos venenosos en las selvas húmedas de la Amazonía del Ecuador. Cincuenta y nueve pacientes recibieron gentamicina y cloranfenicol por vía intravenosa, y cincuenta y cinco pacientes no recibieron tales antibióticos. Todos los demás aspectos de manejo fueron idénticos. No hubo diferencias estadísticamente significativas entre los dos grupos en cuanto a características demográficas, demora en el tratamiento, evidencia clínica y de laboratorio de la gravedad del envenenamiento o el uso de antiveneno. Se presentaron nueve abscesos, seis en el grupo con antibióticos y tres en el grupo sin antibióticos. Los resultados del presente estudio no muestran diferencias estadísticamente significativas en el número de abscesos que se presentaron en los pacientes con y sin tratamiento con antibióticos. Con base en este resultado, no se puede recomendar el uso rutinario de antibióticos profilácticos para la prevención de complicaciones sépticas de la mordedura por crotalídeos venenosos.

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Invited Commentary

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Despite the extraordinary number of pit viper bites around the world each year, there is little consensus on the ideal treatment for patients with major (grade 3 or 4) envenomation. Currently utilized forms of treatment include intravenous administration of antivenin (Crotalidae) polyvalent (Wyeth-Ayerst, Philadelphia, PA, USA) [1], early débridement and intravenous hydrocortisone [2], compression therapy [3], and application of a high voltage, low amperage DC pulse [4].

There is less disagreement on management of the patient in the field or the emergency center, and the administration of broad-spectrum antibiotics and tetanus toxoid (based on tetanus status) is currently recommended [5, 6]. Confirmation of the efficacy of the former in improving outcome is lacking, though local wound infections or abscesses after envenomation are uncommon in published series in the United States [7]. Empiric administration of antibiotics to treat pit viper bites is based on the known bacteriology of rattlesnake venoms [8, 9]. Common gram-positive organisms in the oral cavity of rattlesnakes include histotoxic *Clostridium*, *Streptococcus viridans*, and *Enterococcus*; gram-negative organisms are most commonly *Pseudomonas*, *Proteus*, and *Aerobacter* [9].

The authors are to be congratulated on completing a difficult clinical study. They attempted to determine the effects of administering gentamicin and chloramphenicol in 114 patients with pit viper bites in Ecuador's Amazon rain forest. All identified vipers (38%) were presumably the fer-de-lance, the most common species of the genus *Bothrops* from Mexico to tropical South America. There is also a strong possibility that some bites from members of the genus *Lachesis* (bushmaster) were treated based on the location of the hospital. The bacteriology of the venom of these crotalids is presumably similar to that of the common pit vipers in the United States: *Crotalus* or *Sistrurus* (rattlesnake) and *Agkistrodon* (copperhead and cottonmouth).

Difficulties when interpreting the data include the high probability of a type II error, the more than 6 hour delay in administration of antibiotics in more than 50% of the patients, and the different forms of therapy used (25% without antivenin). Both the delay and need for antivenin were "patient factors" beyond the control of the authors. Yet the lack of efficacy of the broad-spectrum antibiotics in changing outcome is not surprising based on the delays in administration [10]. The same outcome would be likely if such delays in local therapy and administration of antibiotics occurred in patients with deep dog bites, human bites, or penetrating wounds of the gastrointestinal tract. The effect of the antivenin on the results is less clear. There is evidence that radioisotope-labeled antivenin accumulates at the site of the snakebite [11]; the manufacturer states that it "relieves . . . local . . . symptoms"; and anecdotal reports suggest rapid resolution of local edema upon administration of appropriate doses [12]. As neutralization of venom at the site of the snakebite possibly decreases local tissue damage, the risk of infections should also decrease in patients administered antivenin.

The authors have demonstrated that delayed administration of broad-spectrum antibiotics does not change the incidence of local infection after envenomation by pit vipers of the genus *Bothrops* or *Lachesis*. When there is an opportunity for earlier administration of antibiotics, such as in many areas of the southeastern or southwestern United States, it should be done based on the known bacteriology of pit viper venoms. Aminoglycosides are avoided in many trauma centers because of concerns about nephrotoxicity, and a third-generation cephalosporin or a penicillin/β-lactamase inhibitor combination might be used as an alternative. As with all forms of treatment for pit viper snakebites, a prospective randomized study of early administration of antibiotics is needed to validate these recommendations, particularly in light of the reports of antibactericidal activity in venoms as noted by the authors.

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